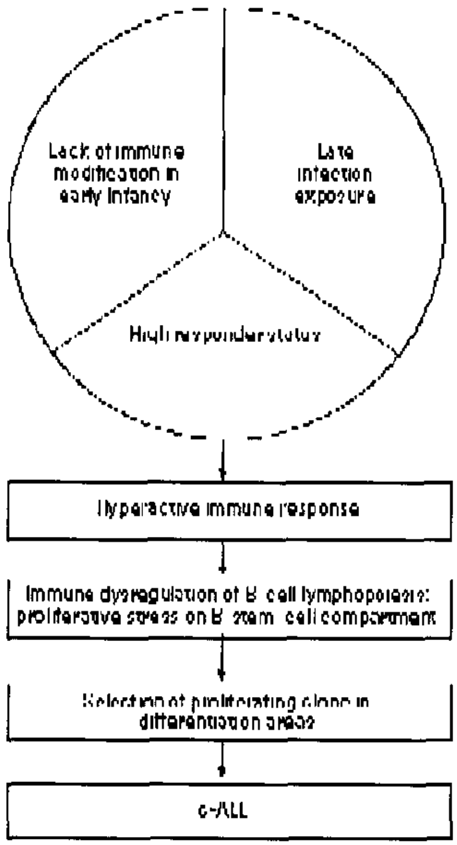
Table 5. Estimated relative risks for the association between neonatal administration of IM vitamin K and childhood cancer

Reference	Country	Study design	All leukemias RR	All leukemias CI	Age range
Golding et al. ([illegible])	England	Case–control	2.35	1.34–5.24	0–14 years
Ekelund et al. ([illegible])	Sweden	Case–control	0.90	0.70–1.16	1 month–13 years
Klebanoff et al. ([illegible])	United States	Case–control	0.47	0.14–1.55	0–7 years
Olsen et al. ([illegible])	Denmark	Cohort	1.00	0.93–1.09	1–13 years
Ansell et al. ([illegible])	England	Case–control	1.00	0.70–2.30	0–14 years
von Kries et al. ([illegible])	Germany	Case–control	0.98	0.64–1.50	1 month–14 years
McKinney et al. ([illegible])	Scotland	Case–control	1.30	0.83–2.03	0–14 years
Farmer et al. ([illegible])	England	Case–control	1.20	0.75–1.92[a]	6 months–14 years
Farmer et al. ([illegible])	England	Ecologic	0.95	0.76–1.17[a]	6 months–14 years
Passmore et al. ([illegible])	England and Wales	Case–control	1.50	0.85–2.86	1–14 years
Passmore et al. ([illegible])	England and Wales	Ecologic	1.13	Not quoted	1–14 years

RR, relative risk.
[a]Acute lymphoblastic leukemia only.


Lack of immune modification in early infancy
Late infection exposure
High responder status
Hyperactive immune response
Immune dysregulation of B cell lymphopoiesis: proliferative stress on B stem cell compartment
Selection of proliferating clone in differentiation areas
c-ALL

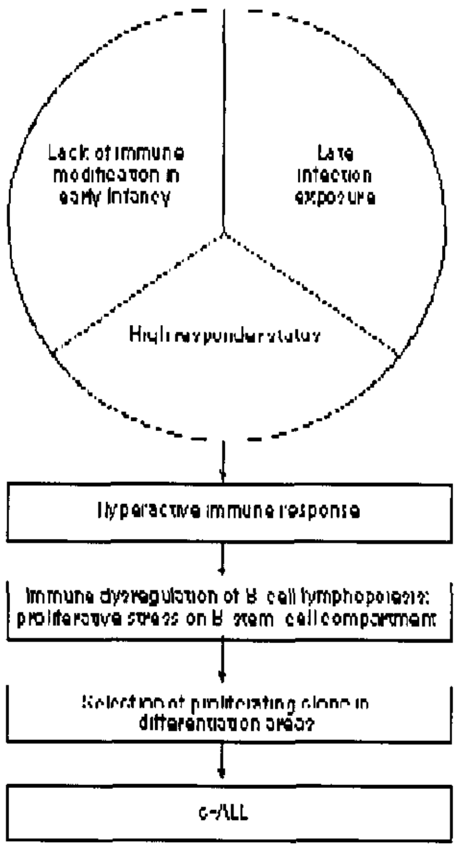

Lack of immune modification in early infancy
Late infection exposure
High responder status
Hyperactive immune response
Immune dysregulation of B cell lymphopoiesis: proliferative stress on B stem cell compartment
Selection of proliferating clone in differentiation arrest
c-ALL

Table 6. Preconceptional carcinogenesis in animals: male exposure followed by mating with an untreated female.

Species/strain	Germ cell stage at exposure[a]	Exposure agent/dose[b]	Site of neoplasms[c]	Reference
Mouse/ICR	1–7 days to 64–90 days; gonia-sperm	X-ray, 216 rad	Lung; significant effects on incidence for 0–14, 15–21, and 14–90 days; on multiplicity for 0–14 days	(227)
Mouse/ICR	GD 9, migrating/dividing gonocytes	X-ray, 216 rad	Lung after postnatal urethane	(133)
	GD 15 dividing gonocytes in genital ridge of testis		(No increase in lung tumors)	
	1–20 days, postmeiotic		Lung, after postnatal urethane	
Mouse/LT	Postmeiotic	X-ray, 504 rad	Lung, leukemia	(229)
Mouse/N5	Gonia		Lung, leukemia	
Mouse/N5	2–14 days, late spermatid/sperm	X-ray, 500 cGy	Leukemia (p = 0.02)	(130)
Mouse/BLR	1–7 days, late spermatids-sperm	X-ray, 4.2 Gy	Lung (increased sensitivity to postnatal urethane); Mammary (decreased latency)	(211)
Mouse/SHT	1–7 days, late spermatids, sperm	X-ray, 4.2 Gy	Skin (TPA-promoted tumors)	(212)
Mouse/C3H	> 50 days, stem cells	X-ray, 600 R	(Lung, females, decreased)	(213)
Mouse/Rf	0–7 days, sperm	X-ray, 250 or 500 cGy	(Lung tumors, no effects)	(214)
	7–14 days, spermatids		(Lung tumors, no effects)	
Mouse/C3H/HeN	0–7 days, sperm	X-ray, 250 or 500 cGy	(Lung tumors, no effects, no increase in sensitivity to urethane)	(225)
	7–14 days, spermatids		(Lung tumors, no effects, no increase in sensitivity to urethane)	
Mouse/CD1	7, 21, 60 days: sperm, late meiosis, gonia	X-ray, 1 or 2 Gy	7 days, [decrease in lung tumors in females]; nonsignificant increase in hematopoietic tumors in females and lung adenocarcinomas in males	(133)
Mouse/N5	0–14 days, late spermatid/sperm	Tritium, 100 or 150 cGy	Leukemia, reduced latency, significant trend with days before mating	(130)
Mouse/C3H × C57BL/6	14 days, spermatids	[illegible] (36% γ-rays) 50, 100 cGy	Liver	(143, 144)
	10 days, gonia		Liver (smaller effect than with 14-day treatment)	
Mouse/C57	15 days, postmeiotic	Co γ, 2 Gy	Liver, p = 0.05; [decreased hepatocyte [illegible]]	(134)
Mouse/BALB	Late fetal gonia	DMBA, 400 µg/mouse	(No effect)	(135)
Mouse/CD1	GD 17, nondividing oocytes	Diethylstilbestrol, 1 mg/kg	Uterus (sarcoma); lymphoma; ovary (granulosa-theca cell and tubular adenoma); (No changes in male offspring)	(136)
Mouse/ICR	GD 17, nondividing oocytes	Urethane, 1.5 g/kg	(No increase in lung tumors)	(133)
Mouse/ICR	1–14 days, late spermatids-sperm	Urethane, 1.5 g/kg	Lung	(137)
	25–35 days: gonia, early meiosis		Lung	
	21–42 or 50–56 days: gonia		Lung	
	91–100 days: stem cells		(No effect on lung tumors)	
Mouse/C3H	7, 61, 67 days	Urethane, 1 g/kg	(No increase in lung or liver tumors); nonsignificant increase in hematopoietic tumors in females	(138)
Mouse/CD-1	7 days, sperm	Urethane, 1.75 mg/kg	Liver (male offspring only)	(139)
Mouse/NIH Swiss	14 days, spermatids	Urethane, 1.5 g/kg	Adrenal pheochromocytoma; preneoplastic hyperplasia of glandular stomach; lymphoma (females); [decrease in histiocytic sarcoma]	(140)
Hamster/SG	Fetal day 12	NDEA, 10 mg/kg	(No effect)	(141)
	Fetal day 13		Larynx/trachea, neuroendocrine tumors, increased ratio malignant/benign, increased multiple tumors; increased uterine tumors, lymphoma	
	Fetal day 14		Larynx/trachea, neuroendocrine tumors, increased ratio malignant/benign, increased multiple tumors, increased uterine tumors, lymphoma	
Hamster/SG	Fetal day 15	NDEA, 10 mg/kg	(No effect)	(213)
Rat/BDIV	2 weeks, spermatid	ENU, 60 mg/kg	Nervous system	(120)
	7 days (sperm), 21 days (spermatocytes) or 28 days (spermatogonia)		Nervous system, nonsignificant increase	
Rat/BDIV	1, 14, 21 or 28 days	ENU, 40 mg/kg	(Nervous system no effect) [Thyroid, nonsignificant higher time-effect correlation]	(137)
Rat/SD	Continuous for 70 days (spermatocytes, spermatids, sperm)	Cyclophosphamide, 2.5–5.0 mg/kg daily	Thymus (not all tumors diagnosed)	(138)
Mouse/NIH Swiss	14 days, spermatids	Chromium chloride, 1 mmol/kg	Adrenal pheochromocytoma; lung (females); thyroid; Harderian gland	(140)
Rat/LIO	Fathers 3 or 25 months old	No treatment; age as variable	Offspring treated with methylnitrosourea, 20 mg/kg, at 30 months: shorter survival of tumor-bearing offspring of older fathers	(219)

Abbreviations: DMBA, 7,12-dimethylbenz[a]anthracene; ENU, ethylnitrosourea; NDEA, N-nitrosodiethylamine; TPA, 12-O-tetradecanoylphorbol 13-acetate.
[a]Information in this column indicates the spermatogenic stage of the germ cells at which exposure occurred. For fetal exposures, GD is gestation day; for adults, days is days before mating. [b]Unless otherwise indicated, one treatment was given at each of the times indicated. [c][illegible] effects are listed, usually of statistical significance; [ ] bracket negative effects; ( ) bracket no change.

Table 7. [illegible]

Species/strain	[illegible]	Exposure [illegible]	Site of neoplasm	Reference
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]		[illegible]	
	[illegible]		Lung	
	[illegible]		[illegible]	
Mouse/[illegible]	[illegible]	[illegible]	Lung [illegible]	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	Lung	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	Lung	[illegible]
Hamster/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

[illegible]

Species/strain	Exposure period	Agent/dose	Sensitivity		Reference
			Range	Highest	
Mice, [illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
Mice, [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mice, [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Table 9. Lung/upper airway tumors after transplacental or neonatal exposures in animals.

Species/strain	Exposure period[a]	Agent/dose[c]	Sensitivity[b] Range	Sensitivity[b] Highest	Reference
Mouse/B6/HT	GD 12 or 16–18	X ray, 200 R	GD 16–18	GD 16–18, fewer lung tumors in male offspring from GD 12	(150)
Mouse/B6C3	GD 17–PN 35	1x ray, [illegible] Co 3.8 Gy	GD 17–PN 35	GD 17	(160)
Mouse/ICR	GD 0–16, or PN 1, 1x	X ray, 36 Rad, then urethane on PN 21	X ray alone, no effect; Increased susceptibility to urethane, GD 0–14	No significant differences	(296)
Mouse/NMRI	GD 12–16, 1x	5-Azacytidine, 1 or 2 mg/mouse	GD 14 (2 mg only), 16	GD 16	(210)
Mouse/NMRI	GD 6–20, 1x	DMBA, 60 mg/kg	GD 10–20	GD 15–20	(198)
Mouse/A/C 5	GD 17–21, 1x	Urethane, 25 mg/mouse	17–21	<8 hr before birth	(279)
Mouse/ICR	GD 6–PN 5, 1x	Urethane, 1 g/kg	GD 10–PN 5	GD 15–19	(169)
Mouse/ICR	GD 7–19, 1x	Urethane 1 or 0.2 g/kg	GD 17–19	GD 15, 17, 19 or <12 hr before birth	(158)
Mouse/ICR	GD 9–17, 1x	4-NQO, 25 mg/kg	GD 12–17	GD 17	(158)
Mouse/[illegible]	Daily GD 6–11, 11–15, or 14–19	Urethane, 1.5 g/kg	GD 11–15 and 14–19	GD 14–19	(153)
	GD 12, 15, and 18 or PN 1, 4, 7, 15, 18, and 21		PN 1–21	—	
Mouse/[illegible]	GD 9–17, 1x	Methylnitrosourethan, 5 mg/kg	GD 9	—	(159)
Mouse/[illegible]	GD 12, 14, 16, or 18	ENU, 60 mg/kg	All groups	GD 16	(159)
Mouse/B6C3	GD 12, 14, 16 or 18 or PN 1, 15 or 42	ENU, 60 mg/kg	All groups	GD 16	(148)
Mouse/B6	GD 14, 15, or 17	ENU, 0.5 mmol/kg	All groups	GD 15	(292)
Mouse/C3H eB/FeJ	GD 10, 13 or 15 adult	ENU 10, 25 or 50 mg/kg	GD 10–15	GD 15; Size greatest on GD 10	(170,207)
Mouse/C3H eB/FeJ	GD 13–19 1x or PN 5, 15 or 35	ENU, 50 mg/kg	All groups	GD 16 and PN 5; More papillary tumors after GD 13–16 and PN 5 versus GD 17–19; Size greatest, GD 13	(298)
Mouse/C3H/HeCr	GD 11, 16, or 10	ENU, 0.5 mmol/kg	All groups	Size and progression greater for GD 11 and 16; Postnatal increase in multiplicity only after GD 10	(198)
Mouse/[illegible]	GD 15–19 1x	ENU, 0.75 mmol/kg	All groups	GD 15, number of tumors; GD 15, size of tumors	(154)
Mouse/C3H	GD 16 or 19	MNU, 7.4 mg/kg	GD 19	—	(196)
		MNU, 5.1 mg/kg	GD 19	—	
		ENU, 4.6 mg/kg	GD 16 or 19	GD 16	
Mouse/A/HE, SWR, BALB, C57BL/6, 129/Sv	GD 12–19, 1x	ENU, 0.5 mmol/kg	A/HE, GD 14–19	GD 16	(278)
			SWR, GD 12–18	GD 16	
			BALB, GD 14–18	GD 16	
			C57BL/6, GD 14–18	GD 16	
			129/Sv, GD 14–18	GD 16	
Mouse/B6C3 and C3B6	GD 12–16 1x	ENU 0.5 mmol/kg	GD 12–16	GD 16	(220)
Mouse/C3H/MA/Kf	GD 14–18 1x	NDEA, 50 mg/kg	GD 16–18	GD 18	(240)
Mouse/NIH Swiss	GD 15, 17 and 19 or PN 1, 4, 7, 10 and 14	NNK, GD 100 mg/kg; PN 50 mg/kg	PN	—	(120)
Mouse/NIH Swiss	GD 12–18 or PN 1–8	AZT, GD 12.5 or 25 mg/mouse or PN 25, 50, 100 or 200 mg/kg	GD 12–18 and PN 1–8	No significant differences	(270)
Hamster/SG	GD 10–15 1x	NDEA, 45 mg/kg	GD 12–15 trachea, larynx, and lung tumors	GD 15	(160,169,217)
Hamster/SG	GD 12–14	NDEA, 14 mg/kg	GD 14, trachea, larynx (papillomas and neuroendocrine)		(168)
Hamster/SG	GD 0, 10, 12, or 14	2-Hydroxypropyl-propylnitrosamine; 2-oxopropyl-propylnitrosamine 100 mg/kg[d]	GD 14, laryngotracheal papillary polyps		(168)
Hamster/SG	GD 9–15, 1x	[illegible] saline, 30 mg/kg	Tracheal and larynx: all groups	No significant differences	(342)

Category of lung: [illegible] [illegible] lung buds appear; 11: bronchial divisions in right lung; 14: [illegible] [illegible]; 12–16: pseudoglandular, undifferentiated; 16: alveoli appear, growth rate [illegible] [illegible] [illegible] [illegible]; 15: fully functional lung.

Abbreviations: AZT, 3'-azido-3'-deoxythymidine; DMBA, 7,12-dimethylbenz[a]anthracene; 4-NQO, 4-nitroquinoline-N-oxide; [illegible]; MNU, N-nitroso-N-methylurea; NDEA, N-nitrosodiethylamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PN, days after birth.

[a]Sensitivity range indicates the ontogenetic period during which exposure led to the appearance of significant numbers of lung tumors in the adult offspring. [illegible] [b]Sensitivity highest indicates the period during which the greatest number of lung tumors was [illegible]. [c]GD or PN of exposure are indicated; [illegible] single exposure on each of the days indicated. [illegible] [d][illegible]

Table 10. [illegible]

Species/strain	Exposure period	Agent/dose	Sensitivity: Range	Sensitivity: Highest	Reference
Mice, [illegible]	GD [illegible]	X-ray [illegible]	GD [illegible]	—	[illegible]
Mice, [illegible]	GD [illegible]	X-ray [illegible]	GD [illegible]	—	[illegible]
Mice, [illegible]	GD [illegible]	[illegible]	All gonads	[illegible]	[illegible]
Mice, [illegible]	GD [illegible]	DMBA, [illegible]	Granulosa cell tumors [illegible]	[illegible]	[illegible]
Mice, [illegible]	GD [illegible]	Urethane, [illegible]	[illegible]	No significant difference	[illegible]
Mice, [illegible]	GD [illegible]	Urethane, [illegible]	All gonads: granulosa cell tumors and tubular adenomas	[illegible]	[illegible]
Mice, [illegible]	GD [illegible]	ENU, [illegible]	All gonads [illegible]	[illegible]	[illegible]
Mice, [illegible]	GD [illegible]	ENU, [illegible]	All gonads	[illegible]	[illegible]
[illegible]	GD [illegible]	[illegible]	All gonads: [illegible]	[illegible]	[illegible]
Mice, [illegible]	GD [illegible]	[illegible]	GD [illegible]	[illegible]	[illegible]
Mice, [illegible]	GD [illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Table 11. Lymphoid neoplasms after transplacental or neonatal exposures in animals.

Species/strain	Exposure period[b]	Agent/dose[c]	Sensitivity[a] Range	Sensitivity[a] Highest	Reference
Mouse/RF	GD 17–PN 180 1x	X-ray, 100, 200 or 300 R	Thymic lymphoma: PN 1–180 Myeloid leukemia: PN 14–180	PN 40 PN 30	(154)
Mouse/B6/WHT	GD 12 or 16–19	X-ray, 200 R	GD 12: decrease in nonthymic lymphoma and reticulum cell sarcoma	—	(190)
Mouse/B6C3	GD 17, PN 0–364, 1x	γ-Rays, [137]Cs, 3.8 Gy	Lymphoma: PN 0–105 Histiocytic sarcoma decrease, GD 17–PN 240 Myeloid leukemia, PN 35–365	PN 35 GD 17 PN 105	(155)
Mouse/BALb	GD 14 or adult	α-Radiation, [241]Am, 100, 500 or 1,500 Bq/g (GD) or 45–213 Bq/g (PN)	GD 14: males only	—	(243)
Mouse/NMRI	GD 5–20, 1x	DMBA, 60 mg/kg	GD 6–15	GD 11 (males), GD 6–11 (females)	(197)
Mouse/B6C3	GD 12, 15, and 18; or PN 1, 4, 7, 15, 18 and 21	Urethane, 0.5 g/kg	PN 1–7	PN 1–7	(153)
Mouse/B6C3	GD 12, 14, 16 or 18, PN 1, 15, or 42	ENU, 60 mg/kg	GD 16–PN 42	PN 42	(153)
Mouse/DBA/2J, C57BL/6J, C57L/J, SWR/J	GD 12, 14, 16, or 18	ENU, 0.5 mmol/kg	DBA/2: GD 14–18 C57BL/6J: GD 14–18 C57L/J: GD 14–18 SWR: GD 12–18	GD 16 GD 16, 18 GD 16, 18 All similar	(228)
Mouse/B6C3	GD 12, 14, 16, or 18; PN 1, 15, or 42	ENU, 60 mg/kg	GD 12–PN 42	GD 16, PN 42 (terminated at 35 weeks)	(153)
Mouse/B6C3	GD 12, 14, 16 or 18 or PN 1, 15 or 42	ENU, 60 mg/kg	GD 12–PN 42	Males: PN 42 Females: PN 15, 42 (structural death)	(196)
Mouse/NIH Swiss	GD 16 or 19	NDMA, 0.1 mmol/kg	Histiocytic sarcoma: GD 19	—	(193)
Mouse/Swiss	GD 1–7, 8–14, or 15–22	Carbendazim, 500 mg/kg + nitrite, 0.05% DW	GD 1–7, 8–14 or 15–22	No significant difference	(244)
Mouse/NMRI	GD 12, 14 or 16	5-Azacytidine, 1 or 2 mg/kg	GD 12, 1 mg/kg and GD 16, both doses: leukemia/lymphoma increase GD 12, 2 mg/kg and GD 14, both doses: leukemia/lymphoma decrease vs. controls	Increase, GD 16, 1 mg/kg Decrease: GD 14, 2 mg/kg	(210)
Mouse/CD-1 Swiss	GD 12–18 or PN 1–8	AZT, GD 12.5 or 25 mg/mouse PN 25, 50, 100, 200 mg/kg	Histiocytic sarcoma, females GD 12–18 only Lymphoma (lymphoblastic follicle center cell), decreased, both sexes and dose periods	—	(233)
Dog/beagle	GD 8, 28 or 55 or PN 2	γ-Ray, [60]Co, 16 or 83 cGy	Lymphoma/leukemia: GD 55	—	(245)

Ontogeny of the lymphoid system Mouse—GD 11–12: first appearance of thymus; 13: lymphocyte precursor seen in thymus; 14–15: rapid growth and histogenetic and organogenetic change in thymus; 15: myelopoiesis in spleen; 16: myelopoiesis in marrow; 17: thymus versus adult: 10% of leukocytes, 50% of lymphocytes, 200% more young lymphocytes; 18: thymus starts size.
Abbreviations: AZT, 3′-azido-3′-deoxythymidine; DMBA, 7,12-dimethylbenz[a]anthracene; DW, drinking water; NDMA, N-nitrosodimethylamine; PN, days after birth.
[a]Sensitivity range indicates the ontogenetic period during which exposure led to the appearance of significant numbers of hematopoietic neoplasms of the type indicated in the adult offspring. Sensitivity highest indicates the period during which the greatest numbers of hematopoietic neoplasms were induced. [b]GD or PN of exposure are indicated; 1x indicates a single exposure on each of the days indicated. [c]The dose at each exposure is given.

Table 12. Nervous system tumors after transplacental or neonatal exposures in animals.

Species/strain	Exposure period[b]	Agent/dose[c]	Sensitivity[a] Range	Sensitivity[a] Highest	Reference
Mouse/B6C3 and C3B6	GD 12–18, 1x	ENU, 0.5 mmol/kg	GD 12–18	GD 12–14	(226)
Mouse/C3H/HeN	GD 12, 13, 14, 16, or 18	ENU, 0.5 mmol/kg	GD 12–14	No significant difference	(246)
Mouse/C3H/HeNC MTV-	GD 15 or 19	ENU, 0.4 mmol/kg	Schwannomas: both groups; Glioblastomas: GD 19	GD 19	(248)
Rat/EDDX	GD 9–16 or 16–22	ENU, 0.5 mmol/kg	GD 16–22	—	(249)
Rat/EDDX	GD 6–22, 1x	ENU, 20 mg/kg	GD 11–20	GD 15–22	(250)
Rat/EDDX	GD 12–20, 1x	ENU, 0.5 mmol/kg	GD 13–20	GD 15–20	(249)
Rat/EDDX	GD 15 or 22	ENU, 5 mg/kg	Both groups	No significant difference	(107)
Rat/Wistar	GD 15, or PN 1–28, 1x	ENU, 40 mg/kg	Gliomas and glioependymomas: all groups	GD 15	(223)
Rat/EDDX	GD 15 or 22	ethylnitrosobiuret, 100 mg/kg	Both groups	No significant difference	(107)
	GD 15 or 23	1-phenyl-3,3-dimethylhydrazine, 25 mg/kg	Both groups	GD 23	
	GD 11 or 22	Azoxymethane, 30 mg/kg	GD 22	—	
	GD 15 or 21	methyl-2-benzylhydrazine, 40% of LD_{50}	Both groups	GD 21	
	PN 1, 3, 10, 30, or 60 or adult	Azoxymethane	All groups	PN 1	
Rat/Wistar	GD 12, 14, 17, or 19	MNU, 40 mg/kg	GD 14	—	(221)
Hamster/SG	GD 3–14, 1x	ENU, 0.2 or 0.5 mmol/kg	GD 9–14	Females: PNS tumors shorter latency with GD 9–11; Other: both sexes and doses GD 14	(224)
Opossum	PN 0, 7, 14, 21, 28, 46, 55, 70, 84, or 112	ENU, 100 mg/kg	Intraocular medulloepitheliomas: PN 7–20; Brain gangliogliomas: PN 0	No significant difference	(102)
Rabbit	GD 9 or 10, or 16–19 or 15–24	ENU, 30 mg/kg (GD 9, 10) or 60 mg/kg (GD 10–19, 15–29)	Gliomas, schwannomas: all groups	GD 9	(225,226)

Ontogeny of the nervous system: Mouse—GD 10.5: brain divisions apparent, spinal cord well differentiated; 11: rapidly proliferating neuroblasts, cranial and spinal ganglia formed. Spinal cord more organized; 14: structures of brain in place (olfactory lobes, cerebellum, pituitary, etc. discernible); 15: rapid growth of cerebrum. Rat—GD 9.5: neural plate appears; 11: three brain vesicles present; 13: cerebral vesicles present, choroid plexuses in lateral, second, and fourth ventricles; 15: choroid plexus in third ventricle; 17: choroid fissure completely closed; 20: corpora quadrigemina recognizable in the mesencephalon. Hamster—GD [illegible]: brain divisions apparent; fifth and combined seventh/eighth cranial nerve ganglia appear; 10: beginning of growth and differentiation. Rabbit—GD 8: neural plates appear; 10: neural tube closes, three brain vesicles appear; 11: cerebral hemispheres appear; 15: olfactory bulb formed, cerebellum recognizable.

Abbreviations: LD_{50}, median lethal dose; MNU, methylnitrosourea; MTV, mammary tumor virus negative; PN, days after birth; PNS, peripheral nervous system.

[a] Sensitivity range indicates the ontogenetic period during which exposure led to the appearance of significant numbers of neurogenic tumors of the types indicated in the adult offspring. Neurogenic tumors in mice after perinatal ENU were, in order of frequency of type: neurinomas, oligodendrogliomas, medulloblastoma, astrocytoma, other; in order of frequency of site: peripheral and cranial nerves, cerebrum, spinal cord, pons, cerebellum, cauda, and meninges. Sensitivity highest indicates the period during which the greatest number of neurogenic tumors were initiated. [b] GD or PN of exposure are indicated. 1x indicates a single exposure on the days indicated. [c] The dose at each exposure is given.

Table 13. [illegible]

Species/strain	Exposure period	Agent/dose	Sensitivity: Range	Sensitivity: Degree	Reference
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
			[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Table 14. [illegible]

Species/strain	Exposure period	Agent/dose	[illegible] Range	[illegible] Highest	Reference
Mice, [illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
Mice, [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mice, [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rat, [illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]

[illegible]

Table 15. [illegible]

Tissue	Species/strain	Exposure period[b]	Agent/dose[c]	Sensitivity[a] Range	Highest	Reference
Forestomach	Mice/[illegible]	GD 5–[illegible]	[illegible] mg/kg	GD [illegible]	[illegible]	[illegible]
[illegible]	Mice/[illegible]	PND 15–[illegible]	[illegible] mg/kg	All groups	PND 15–[illegible]	[illegible]
Prostate	[illegible]	GD [illegible]	[illegible] mmol/kg	GD [illegible]	No significant difference	[illegible]
Testis	Rat/[illegible]	GD [illegible]	[illegible]	[illegible] GD [illegible]	No significant difference	[illegible]

[illegible]

[a] [illegible]

			Sensitivity		
Species/strain	Exposure period	[illegible]	Range	Highest	Reference
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	–	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 17. Liver tumors after transplacental or neonatal exposures in animals.

Species/strain	Exposure period[b]	Agent/dose[c]	Sensitivity[a] Range	Sensitivity[a] Highest	Reference
Mouse/B6C3	GD 17, 3 months, or 9 months	X ray 0.5–7 Gy Neutron, 0.03–2.14 Gy	X ray: all groups Neutrons: GD 17, 3 months	X ray: 3 months Neutrons: GD 17	(227)
Mouse/B6WHT	GD 17, PN 0 or 5 weeks	X ray GD 150 or 300 R PN 400 R	All groups ≥ 300 R	PN 0	(228)
Mouse/B6C3	GD 17, PN 0–365	γ ^{137}Cs 1–5.7 Gy	GD 17–PN 35	PN 0, 7	(165)
Mouse/NMRI	GD 6–20 1x	DMBA, 60 mg/kg	GD 6–20 (males)	GD 14–20	(159)
Mouse/B6C3	GD 12–20 or PN 1–21	Benzidine, 150 ppm diet	Males: both groups	PN	(169)
	GD 12–20 or PN 1–21	Safrole, 120 mg/kg	Males: both groups	PN	
Mouse/ICR	GD 7, 9, 11, 13, 15, or 17	Urethane, 0.5 or 1 g/kg	GD 11–15	GD 13	(229)
Mouse/ICR	GD 7–19	Urethane 1 or 3.2 g/kg	GD 11–15, 19 if < 12 hr before birth	GD 13	(198)
Mouse/B6C3	GD 7–11, 11–15, or 14–19	Urethane, 0.5 g/kg	GD 11–18	GD 14–18	(193)
	GD 12, 14, 16, or 18	ENU, 60 mg/kg	GD 12–18	GD 17–18 (euthanized at 36 weeks)	
Mouse/B6C3 or C3B6	GD 12, 14, 16, or 18	ENU, 60 mg/kg	GD 12–18	No significant differences (natural death)	(220)
Mouse/B6C3	GD 12, 14, 16, or 18 or PN 1, 15, or 42	ENU, 60 mg/kg	All groups	PN 1, 15	(169)
Mouse/C3HeB	GD 10, 13, or 15	ENU, 10, 25, or 50 mg/kg	GD 10–15	Males: GD 15. Liver tumor size greatest after GD 10, and more microvasculature invasion Females: GD 13	(230)
Mouse/NIH Swiss	GD 15, 17, and 19 or PN 1, 4, 7, 10, and 14	NNK, GD 100 mg/kg, PN 50 mg/kg	Males: both groups	PN	(221,222)
Mouse/NIH Swiss	GD 15, 17, and 19 or PN 4 GD 19 or PN 4 or PN 50 mg/kg	NNK, GD 100 mg/kg PN 50 mg/kg NDMA, GD 10 mg/kg	Males: PN 4 Females: no effect Males: PN 4 Females: PN 4	—	(152)
Mouse/C3H	GD 16 or 19	NDMA, 7.4 mg/kg NDEA, 51 mg/kg ENU, 47 mg/kg	Males: GD 19 Females: GD 16, 19; males: GD 19 Females: GD 19	— No difference —	(193)
Mouse/B6C3	PN 1 or 15 mg/kg	NDEA, 1.5, 5, or 10 mg/kg	Males: all	1.5 mg/kg: PN 15 5 or 10 mg/kg: no difference	(169)
Mouse/NMRI	GD 12, 14, or 16	5-azacytidine, 1 or 2 mg/mouse	GD 12–16 (males) GD 12 (2 mg) or 14 (1 mg) (females)	No significant differences	(219)
Mouse/CD-1	GD 12–18 or PN 1–8	AZT, GD 12.5 or 25 mg/mouse or PN 25, 50, 100, 200 mg/kg	Females: GD 12–18 and PN 1–8	No significant differences	(233)
Rat/BDIX	GD 16 or 22	NDEA, 70 or 150 mg/kg	GD 22	—	(167)
Hamster/SG	GD 6–4, 1x	ENU, 0.5 mmol/kg	GD 11–15: cholangiocarcinomas All groups: hemangiosarcomas	GD 14–15	(224)

Ontogeny of liver: Mouse—GD 9: liver primordia with foregut diverticulum by day 9; 10: discernible liver with epithelial cords, evidence of hematopoiesis by 10.5; 12: many blood cells; 12–15: rapid growth to fill half the body cavity by day 15; 16: still mainly hematopoietic. Rat—GD 11: hepatic diverticulum is formed; 12: epithelial cords begin to appear; 14: adult configuration. Hamster—GD 8.5: two small liver diverticula appear, along with a few scattered liver cords and hepatic sinusoids; 9–11: right and left lobes evident, size increases, ducts open into the gut, gall bladder primordium appears; 12: gall bladder separates from liver, liver increasingly dense, with well-formed capsule.
Abbreviations: AZT, 3′-azido-3′-deoxythymidine; DMBA, 7,12-dimethylbenz[a]anthracene; NDMA, N-nitrosodimethylamine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PN, days after birth.
[a]Sensitivity range indicates the ontogenetic period during which exposure led to the appearance of significant numbers of liver tumors in the adult offspring. Unless otherwise specified, these were hepatocellular tumors. Sensitivity highest indicates the period during which the greatest numbers of liver tumors were initiated. [b]GD or PN of exposure are indicated; 1x indicates that exposure was given once, on each of the indicated days. [c]The dose at each exposure is given.

Table 18. [illegible]

Species/Strain	Exposure period	[illegible]	Sensitivity: Range	[illegible]	Reference
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
Mouse/[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rat/Wistar	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rat/SD	[illegible]	[illegible]	[illegible]	—	[illegible]
Rat/SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

[illegible]

Species/Strain	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Table 20 [illegible]

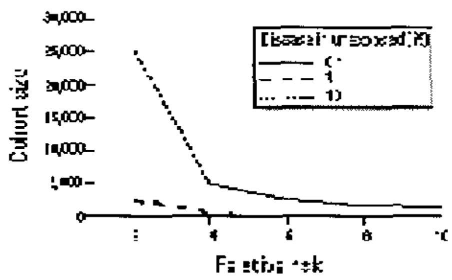
Species/strain	Exposure period	[illegible]	[illegible] Range	Highest	Reference
[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]

[illegible]

Table 21. [illegible]

[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
			[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	— [illegible]	[illegible]

[illegible]



Cohort size
30,000
25,000
20,000
15,000
10,000
0